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(54) Title: METHOD OF MANUFACTURE FOR TRANSDERMAL MATRICES

(57) Abstract

A method of manufacture for the production of transdermal drug delivery matrices and devices, transdermal sampling devices, and dermal conditioning devices. A polymer and an active agent are mixed and heated in a multiple–lobed compounder to produce a polymer mixture. The polymer mixture is extruded and then at least a portion of the extrudate is formed into, for example, the transdermal drug delivery matrix, or incorporated into the transdermal drug delivery device. These alternative methods for preparing transdermal matrices have several advantages over the current methods of manufacture. The matrix components, particularly the active agent, are not exposed to extremes in solvent or temperature for extended periods of time during the manufacture process. The transdermal matrices prepared by these methods perform better in transdermal devices and show greater flux of active agent. As a result of the improved performance, less active agent may be utilized during the manufacturing process, and smaller or thinner transdermal matrices may be produced for incorporation into the corresponding transdermal device.

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METHOD OF MANUFACTURE FOR TRANSDERMAL MATRICES

Field of the Invention

The present invention relates to novel methods of manufacture for the production of transdermal drug delivery matrices and devices, transdermal sampling devices, and dermal conditioning devices.

Background Art

Solvent casting techniques have been the preferred method of manufacture for transdermal matrices. This method of manufacture requires the use of one or more "casting" solvents for manipulation of the desired polymeric matrix components. The polymer, the active agent, and other excipients to be incorporated into the transdermal device are dissolved or suspended in the casting solution. The polymer mixture is distributed, or "cast," onto a support layer and the solvents are removed during a heating or drying process. The resulting solvent-free matrix is then further processed into a transdermal drug delivery device. If the desired active agent is inert with respect to the casting solvents, it may be incorporated into the matrix during the solvent casting procedure (see, for example, U.S. Patent No. 4,906,463 to Cleary et al.). If the active agent is not stable under the solvent conditions, the transdermal matrix may be solvent cast in the absence of the active agent, which may then be added in a later step. For example, the active agent may be incorporated by adding the agent to a "reservoir" cavity in the polymeric matrix, as described in U.S. Patent No. 4,588,580 to Gale et al. Alternatively, the active agent may be "printed" onto the matrix, as described in U.S Patent No. 4,915,950 to Miranda et al.

While solvent casting techniques avoid any potential thermal degradation of the active agent through the use of chemical instead of temperature means to manipulate the polymeric components, the processes are fairly time-intensive and expensive. Large quantities of costly solvents are utilized, which must subsequently be evaporated away from the polymeric matrix prior to further processing. The evaporation step often requires lengthy coating lines, specialized drying ovens, long evaporation times, and additional procedures for solvent disposal or reclamation. Formulations must be optimized with respect to which solvents are compatible with

the desired polymers and active agents, and the possibility of chemical reactivity may limit formulation options. In addition, the solvents used during the casting process must be removed without substantially changing the matrix composition, a particular challenge if the active agents or other important components are somewhat volatile or temperature-sensitive.

Silicone adhesives are one pressure-sensitive adhesive commonly used in transdermal devices (see, for example, U.S. Patent No. 5,232,702 to Pfister et al.). These adhesives have been shown to be non-irritating and non-sensitizing to the skin, and thus are acceptable for topical use. The silicone adhesive is generally formulated via solvent casting, using any of a number of organic solvents to dissolve or suspend the silicone during the manufacture of the transdermal matrix.

Polyisobutylene adhesives are another pressure-sensitive adhesive commonly used in transdermal devices (see for example, U.S. Patent No. 5,128,124 to Fankhauser et al.). These polymers do not lose their cohesive properties upon exposure to oily, nonpolar compounds (active agents, enhancers, and the like) that generally incapacitate other pressure-sensitive adhesives. However, the high viscosity of the polyisobutylene polymers makes incorporation of the active agent difficult. In addition, the nonpolar nature of polyisobutylene tends to limit its drug-carrying capacity, such that these polymers can be relatively impermeable to the more polar active agents. Furthermore, while many other transdermal matrices can be easily prepared by solvent casting, removal of the casting solvents from polyisobutylene-based polymers is problematic, due to the low solvent diffusion rates. Despite these disadvantages, polyisobutylenes have been employed to a limited extent in the preparation of transdermal devices, as described in, for example, US Pat. No. 5,059,189 to Cilento et al. and PCT publication WO 96/40355 to Jona et al. However, the polyisobutylenes are generally used as an in-line adhesive or separating layer in transdermal systems, but not as the drug-containing polymeric matrix itself (see, for example, U.S. Patent Nos. 4,906,169 to Chien et al. and 5,508,038 to Wang et al.).

Single screw extrusion processes have an advantage over solvent casting, in that the use of solvents during the manufacture process is decreased or even eliminated, along with the relatively high energy and equipment costs associated with such processes. However, these manufacturing processes have been used with limited

success in the area of transdermal drug delivery. The amalgamation produced by a typical single screw extruder is insufficient to provide a consistent composition for use as a transdermal drug delivery device. Furthermore, many drugs cannot withstand exposure to the high temperatures and extended lengths of time that are necessary to achieving adequate mixing via the typical single screw extrusion process. This observation is particularly true when using dense polymeric components, for example polyisobutylenes and silicones.

Thus, alternative methods for preparing transdermal matrices that do not expose the incorporated active agent to extremes in solvent or temperature for extended periods of time would be advantageous.

Summary of the Invention

The present invention relates to a novel method of manufacturing a transdermal drug delivery matrix and alleviates many of the difficulties currently faced during the preparation of transdermal drug delivery matrices. In addition, the present method of manufacture yields uniform compositions of transdermal polymer mixtures containing an active agent, prepared without using large quantities of solvents, and without loss of the active agent due to exposure to temperature variations. The transdermal matrices prepared by these methods perform better in transdermal devices and show greater flux of active agent. Flux improvements of greater than about 10%, preferably greater than about 20%, and more preferably greater than about 40% may be measured from matrices prepared by the method of the present invention. As a result of the improved performance, less active agent can be utilized during the manufacturing process, and smaller or thinner transdermal matrices can be produced for incorporation into the corresponding transdermal device.

One aspect of the invention relates to a novel method of manufacturing a transdermal drug delivery matrix, the method comprising the steps of (a) mixing and heating a polymer and an active agent in a multiple-lobed compounder, to produce a polymer mixture; (b) extruding the polymer mixture; and (c) forming at least a portion of the resulting extruded polymer mixture into the transdermal drug delivery matrix.

Another aspect of the invention relates to a novel method of manufacturing a transdermal sampling device, the method comprising the steps of (a) mixing and

heating a polymer and an active agent in a multiple-lobed compounder, to produce a polymer mixture; (b) extruding the polymer mixture; and (c) incorporating at least a portion of the resulting extruded polymer mixture into the transdermal sampling device.

Yet another aspect of the invention relates to a novel method of manufacturing a dermal conditioning device, the method comprising the steps of (a) mixing and heating a polymer and an active agent in a multiple-lobed compounder, to produce a polymer mixture; (b) extruding the polymer mixture; and (c) incorporating at least a portion of the resulting extruded polymer mixture into the dermal conditioning device.

Another aspect of the present invention relates to a novel method of manufacturing a transdermal drug delivery device comprising the steps of (a) blending a polymer and an active agent to produce a polymer mixture, (b) mixing and heating the polymer mixture in a multiple-lobed compounder, (c) extruding the polymer mixture, and (d) incorporating at least a portion of the resulting extruded polymer mixture into a transdermal drug delivery device.

An additional aspect of the present invention relates to the method of manufacturing a contraceptive transdermal drug delivery matrix, the method comprising the steps of (a) blending a pressure-sensitive adhesive, a first portion of a filler, and a hormone to produce a polymer mixture; (b) mixing and heating the polymer mixture and a second portion of the filler in a multiple-lobed compounder; (c) extruding the polymer mixture; and (d) forming at least a portion of the resulting extruded polymer mixture into a contraceptive transdermal drug matrix. One particularly preferred embodiment of the invention relates to the method of manufacturing a contraceptive transdermal drug delivery matrix as described above, wherein the pressure sensitive adhesive comprises polyisobutylene, the active agent comprises a hormone comprising a progestin and an estrogen, the filler comprises polyvinylpyrrolidone and wherein the polymer mixture further comprises an enhancer selected from the group consisting lauryl lactate, diethylene glycol, and combinations thereof.

Other aspects of the present invention relate to the devices produced according to the methods of the present invention, and the use of these devices in transdermal drug delivery, substance sampling,.or dermal conditioning.

Detailed Description of the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular active agents, formulations or transdermal matrices which may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" also include plural referents unless the content clearly indicates otherwise. Thus, for example, reference to "a permeation enhancer" includes not only a single permeation enhancer, but also a mixture of two or more permeation enhancers; reference to "an active agent" includes not only a single active agent, but also mixtures of active agents; reference to "an adhesive layer" includes reference to not only a single adhesive layer but also two or more such layers; and the like.

All publications and references included herein are incorporated by reference in their entirety.

DEFINITIONS

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used herein, the term "transdermal drug delivery device" refers to any device used to administer an active agent by transdermal ("percutaneous") administration as well as transmucosal administration, i.e., delivery by passage of an active agent through the skin or mucosal tissue and into the bloodstream, lymph system, or target tissue.

The terms "subject" or "patient" refer to a human or an animal, usually of the mammal class.

The term "transdermal sampling devices" refers to devices that may be used to sample a desired substance on or within a skin or mucosal surface upon contact of the device with the surface.

The term "dermal conditioning device" refers to a device that alters the physical properties of a biological surface upon application of the device, particularly by the introduction of microperforations in the skin or mucosal surface.

The term "microneedle" refers to a single microprojection or an array of microprojections that, when inserted into the uppermost surface layer, or stratum corneum, of the skin or mucosa, do not cause marked disruption of the underlying dermis layers.

The term "release liner" refers to the removable or strippable layer protecting the adhesive surface of a transdermal device.

The terms "backing", "backing layer" or "backing material" refer to the component of a transdermal device distal to the release liner, and as such define the top face surface of the device.

The terms "matrix" or "polymeric matrix" refer to the layer or layers of polymeric material positioned between the backing material and the release liner.

The term "porous supporting layer" refers to an optional component that may be found embedded within the matrix of a transdermal device. This component may be present to reduce the cold flow of the polymeric matrix, or it may function as a site for deposition of liquid matrix components.

The terms "control release membrane" or "rate-controlling membrane" refer to an optional device component positioned between a reservoir-style drug-containing polymer and the release liner, and functioning to regulate the rate at which an active agent or excipient is released from the reservoir.

The terms "active agent," "agent" or "drug" refer to any beneficial agent or compound that can be administered to produce a beneficial or useful result, and as such broadly include, but are not limited to, any pharmacologically or physiologically active substances for producing a localized effect at the site of administration, or a systemic effect at a site remote from the administration site. A "therapeutically effective" amount of an active agent is meant to describe a sufficient but nontoxic amount of a compound that provides a desired therapeutic effect.

The terms "pressure sensitive adhesive" and "pressure sensitive adhesive polymer" refer to any number of pharmaceutically acceptable adhesives that can be used as a means of securing a device to a surface. These materials adhere to a surface

with slight pressure and release from the surface with negligible transfer of the adhesive to the surface.

The term "about" when associated with a numeric value refers to that numeric value plus or minus 10 units of measure (i.e. percent, grams or degrees), preferably plus or minus 5 units of measure, more preferably plus or minus 2 units of measure, most preferably plus or minus 1 unit of measure.

The term "excipient" refers to an optional component of the polymer mixture other than the polymer and the active agent. Excipients may be, but are not limited to fillers, enhancers, tackifiers, plasticizers, solubilizers, crystallization inhibitors, and cosmetic components. It is commonly understood by one skilled in the art that a given excipient may perform multiple roles within a polymer mixture; for example, the substance may act both as a tackifier and as a plasticizer, or have other functions.

The term "filler" refers to an optional excipient that may be added to a polymer mixture and performs one or more of the following functions: (1) increasing the solubility of active agents and other excipients in the polymer, (2) increasing the water sorption capacity of the polymer, (3) reducing the cold flow of the polymer, or (4) inhibiting crystallization of any of the components of the polymer mixture. The term "cold flow" refers to the viscoelastic flow of a polymer, particularly that which may occur when the polymer is under pressure. As with other excipients, a filler may have additional functions as, for example, an enhancer, a tackifier, a plasticizer, or the like.

The terms "permeation enhancer" or "enhancer" refer to a substance or combination of substances that increase the permeability of a surface of a subject to a pharmacologically active agent. Generally, these act to increase the rate at which the active agent permeates through the skin and into the bloodstream. An "effective" amount of an enhancer refers to an amount that will provide the desired increase in permeability resulting in the desired rate of administration. As with other excipients, an enhancer may have additional functions as, for example, a filler, a tackifier, a plasticizer, or the like.

The term "tackifier" refers to an excipient that is added to an adhesive polymer to increase the tack or stickiness. As with other excipients, a tackifier may have additional functions as, for example, an enhancer, a plasticizer, or the like.

The term "plasticizer" refers to an excipient that acts to plasticize the polymer or polymer mixture and to increase its permeability to the active agent. As with other excipients, a plasticizer may have additional functions as, for example, an enhancer, tackifier, and the like.

The term "high molecular weight polyisobutylene" or "HMW PIB" refers to a polyisobutylene composition typically having an average molecular weight in the range of about 700,000 to about 2,000,000 Daltons. The term "medium molecular weight polyisobutylene" or "MMW PIB" refers to a polyisobutylene composition typically having an average molecular weight in the range of about 60,000 to about 700,000 Daltons. The term "low molecular weight polyisobutylene" or "LMW PIB" refers to a polyisobutylene composition typically having an average molecular weight in the range of about 35,000 to about 60,000 Daltons. The molecular weights referred to herein are weight average molecular weights.

The term "mixing" refers to the step in the manufacturing process of the present invention in which the components of the polymer mixture are mixed in a dispersive manner to a uniform state as these components are transported along a series of modular elements comprising the "length" or the "body" of the compounding device.

The term "dispersive" refers to a style of mixing resulting in a substantially uniform distribution of components in a given volume, as well as the disruption of any aggregates present in the original components and incorporation of the previously aggregated material into the mixture.

The term "extruding" refers to the step in the manufacturing process of the present invention in which the polymer mixture (the "extrudate") leaves the multiple-lobed compounder, usually via one or more dies.

The term "forming" refers to the step in the manufacturing process of the present invention in which the polymer mixture is placed on a surface or laminated between two or more surfaces after the extruding step. The surfaces include, but are not limited to, one or more of the following: a release liner, a backing layer, a porous supporting layer or combinations of the above. Such matrix layers may be "incorporated" into a transdermal drug delivery device, a transdermal sampling device

or a dermal conditioning device by optional further laminating, optionally molding, and cutting the matrix to the desired size and shape.

The term "blending" refers to an optional step in the manufacturing process of the present invention, in which components to be added to the multiple-lobed compounder are combined, or premixed, prior to the mixing step.

The terms "multiple-lobed compounder" or "multiple-lobed compounding device" refer to a multifunctional device capable of continuously mixing the components of a polymeric mixture in a dispersive manner via the interaction of two or more interfaces on modular elements within a series of mixing chambers and extruding the resulting polymeric mixture.

TRANSDERMAL DEVICES

A transdermal drug delivery device, generally in the form of a patch or plaster, comprises a polymeric matrix containing an active agent, a backing layer that is substantially impermeable to the active agent, and a means of securing the device to a surface. The means of securing may be provided by an adhesive overlay, or the polymer itself may be an adhesive. The active agent may be incorporated directly into the polymer, or it may be initially contained in a cavity, or reservoir, within the transdermal matrix. Other excipients, including but not limited to fillers, stabilizers, enhancers or solubilizers may be optionally included in the polymeric matrix to enhance the performance of the device. In addition, other cosmetic or conventional excipients including but not limited to pigments, dyes or fragrances may be optionally added.

Similarly, a transdermal sampling device comprises a polymeric matrix, a backing layer, and a means of securing the device to a surface. Substances from the skin or mucosal surface are "sampled" or absorbed into the transdermal device. The substance may be analyzed within the device, or the device may act as a conduit for transferring the substance to another device for analysis. Examples of transdermal sampling devices may be found, for example, in U.S. Patent No. 3,964,482 to Gerstel et al.

A dermal conditioning device comprises a polymeric matrix, a backing layer, and a means of securing the device to a surface. The surface of the conditioning

device is formed in a manner that contact of the device with a skin or mucosal surface will physically alter the skin or mucosal surface. One manner in which this may be accomplished is by the presence of microscopic needle-like projection or projections on the means of securing side of the dermal conditioning device. Examples of dermal conditioning devices may be found in, for example, PCT publications WO 98/00193 by Eppstein et al. and WO 96/37256 by Godshall et al.

METHOD OF MANUFACTURE

The present invention relates to a novel manufacturing method for the production of transdermal drug delivery matrices, transdermal sampling devices and dermal conditioning devices. The method of manufacture of the present invention is performed as follows.

First, the polymer and filler may be combined in an optional blending, or premixing step, using a mixer such as a Sigma Blade kneader (Jaygo Inc., of Union, NJ). Any number of polymers may be used, but the preferred polymer for use in the present invention is one or more pressure-sensitive adhesives. Such adhesive polymers are well known in the transdermal art. (See, for instance, the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition (1989) Van Nostrand, Reinhold.) Several different types of pressure-sensitive adhesives can be used as a means of securing a transdermal device, including but not limited to polyisobutylenes (PIBs), polyacrylates, silicones, styrene block copolymers (Kratons), and natural gums. Examples of suitable pressure-sensitive adhesives include the following: natural rubber; polybutadienes; polyisobutylenes (for example, those available commercially under the name VISTANEX™ from Exxon Chemical, New Jersey); polyisoprenes; styrene-butadiene copolymers; styrene-isoprene copolymers; styrene-isoprene-styrene block polymers; silicone rubbers including, but not limited to, the polyorganosiloxanes such as polydimethylsiloxane and polydimethyldiphenylsiloxane; polyurethanes; acrylate polymers; methacrylate polymers; and the like. Formulations of silicone adhesives that are useful in transdermal devices include, but are not limited to, those described in U.S. Patent No. 5,232,702 to Pfister et al. and U.S. Patent No. 4,906,463 to Cleary et al. Examples of

suitable natural gums include, but are not limited to, guar gum, acacia gum, karagen, pectin, and the like.

Polymers that are not pressure-sensitive adhesives may also be used in the method of the present invention. Examples of such polymers include, but are not limited to, hydroxypropyl cellulose (HPC), polyester, polyethylene oxide (PEO), polypropylene, poly-L-lactides, polyacrylic acid, acrylics, polyacrylates (for example, Carbopol 934 from B. F. Goodrich), polysulfones, polyvinylpyrrolidone, polyvinylalcohol, starch and starch derivatives, sodium carboxymethyl cellulose and other cellulose derivatives, carbohydrates, polypeptides, xanthan gum, karaya gum, gelatin, etc. High-density polyethylene oxide and polypropylene and other crystalline polymers may be prepared by the present method of manufacture. Combinations of any or all of the above polymers (pressure sensitive or not) are also suitable for the method of manufacture of the present invention. In particular, the water-soluble matrices described in U.S. Patent No. 5,700,478 to Biegajski et al. may be prepared by the method of the present invention. The preferred polymers for use in the method of the present invention are polyisobutylenes and silicones as described in PCT publication WO 96/40355 to Jona et al. and the hydroxypropyl cellulose polymers as described in U.S. Patent No. 5,700,478 to Biegajski et al.

In addition to the polymer itself, the polymer mixture may optionally include a filler, desirable to make manipulation of the components of the polymer mixture easier, as well as to help reduce cold flow in the final product. During the optional blending step, the filler may be added to the polymer in a single portion, or it may be added as first, second, and additional portions, the addition of these filler portions alternating with the addition of any optional excipients. Conversely, the first portion of the filler may be added during the blending step and the second portion may be added during the mixing and heating step. Examples of fillers include, way of example and not for purposes of limitation, polyvinylpyrrolidones (both the soluble and insoluble, or crosslinked, versions), silica gels, polysaccharides, crystalline cellulose, cellulose derivatives including but not limited to carboxyalkyl-celluloses and hydroxyalkyl-celluloses, bentonite, polyaminoacrylates, polyvinyl alcohol, and combinations thereof. Two preferred fillers are the crosslinked-micronized form of polyvinylpyrrolidone (PVP-CLM) available from BASF (Germany), and the Syloid

silica gel powder available from W. R. Grace & Co. (Baltimore, MD). Fillers include, but are not limited to, water absorbing hydrophilic polymers.

An active agent may be combined with the filler prior to the optional blending step. Preferably, the active agent is added to the polymer mixture during the mixing and heating step. Any number of active agents that induce a desired local or systemic effect may be used in the drug delivery devices manufactured by the method of the present invention. In particular, any compound that is suitable for transdermal administration may be employed. Active agents include, but are not limited to, compounds that may be classified as medicines, organic and inorganic drugs, hormones, nutrients, vitamins, food supplements, herbal preparations, and other agents that might benefit a human or animal.

In general, such classifications include, but are not limited to, ACE inhibitors, adrenergics and anti-adrenergics, alcohol deterrents (for example, disulfiram), anti-allergics, anti-anginals, anti-arthritics, anti-infectives (including but not limited to antibacterials, antibiotics, antifungals, antihelminthics, antimalarials and antiviral agents), analgesics and analgesic combinations, local and systemic anesthetics, appetite suppressants, antioxidants, anxiolytics, anorexics, antiarthritics, anti-asthmatic agents, anticoagulants, anticonvulsants, antidiabetic agents, antidiarrheals, anti-emetics, anti-epileptics, antihistamines, anti-inflammatory agents, antihypertensives, antimigraines, antinauseants, antineoplastics, antioxidants, antiparkinsonism drugs, antipruritics, antipyretics, antirheumatics, antispasmodics, antitussives, adrenergic receptor agonists and antagonists, anorexics, appetite suppressants, breath freshening agents (including but not limited to peppermint oil, spearmint oil, wintergreen oil and menthol), cardiovascular preparations (including anti-arrhythmic agents, cardiotonics, cardiac depressants, calcium channel blockers and beta blockers), cholinergics and anticholinergics, contraceptives, cough and cold preparations, diuretics, decongestants, growth stimulants, herbal preparations, hormones including but not limited to androgens, estrogens and progestins, steroids and corticosteroids, hypnotics, immunizing agents, immunomodulators, immunosuppresives, muscle relaxants, neurologically-active agents including anti-anxiety preparations, antidepressants, antipsycotics, psychostimulants, sedatives and

tranquilizers, sore throat medicaments, sympathomimetics, vaccines, vasodilators, vasoconstrictors, vitamins, xanthine derivatives and combinations thereof.

The amount of active agent incorporated will vary, depending on the active agent chosen, the potency of the compound, the intended dosage, the group of individuals undergoing treatment, the particular indication, and the like. Such amounts are easily determined by one of ordinary skill in the art (see, for example, Volume 18 of Drugs and the Pharmaceutical Sciences, titled "Dermatological Formulations: Percutaneous Absorption" (1983) Marcel Dekker, Inc. and the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition (1989) Van Nostrand, Reinhold).

Representative active agents include, by way of example and not for purposes of limitation, bepridil, diltiazen, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitredipine, verapamil, dobutamine, isoproterenol, carterolol, labetalol, levobunolol nadolol, penbutolol, pindolol, propranolol, solatol, timolol, acebutolol, atenolol, betaxolol, esmolol, metoprolol, albuterol, bitolterol, isoetharine, metaproterenol, pirbuterol, ritodrine, terbutaline, alclometasone, aldosterone, amcinonide, beclomethasone dipropionate, betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone, desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol, dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone, fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone, medrysone, 6α-methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tetrahydrocortisol, triamcinolone, benoxinate, benzocaine, bupivacaine, chloroprocaine, cocaine, dibucaine, dyclonine, etidocaine, isobutamben, lidocaine, mepivacaine, pramoxine, prilocaine, procaine, proparacaine, tetracaine, zolamine hydrochloride, alfentanil, choroform, clonidine, cyclopropane, desflurane, diethyl ether, droperidol, enflurane, etomidate, fentanyl, halothane, isoflurane, ketamine hydrochloride, mepridine, methohexital, methoxyflurane, morphine, propofol, sevoflurane, sufentanil, thiamylal, thiopental, acetominophen, allopurinol, apazone, aspirin, auranofin, aurothioglucose, colchicine, diclofenac, diflunisal, etodolac, fenoprofen, fllurbiprofen, gold sodium thiomalate, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meselamine, methyl salicylate, nabumetone, naproxen, oxyphenbutazone, phenacetin,

phenylbutazone, piroxican, salicylamide, salicylate, salicylic acid, salsalate, sulfasalazine, sulindac, tolmetin, acetophenazine, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluorperazine, triflupromazine, disopyramide, encainide, flecainide, indecanide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, tocainide, cisapride, domperidone, dronabinol, haloperidol, metoclopramide, nabilone, prochlorperazine, promethazine, thiethylperazine, trimethobenzamide, buprenorphine, butorphanol, codeine, dezocine, diphenoxylate, drocode, hydrocodone, hydromorphone, levallorphan, levorphanol, loperamide, meptazinol, methadone, nalbuphine, nalmefene, nalorphine, naloxone, naltrexone, oxybutynin, oxycodone, oxymorphone, pentazocine, propoxyphene, isosorbide dinditrate, nitroglycerin, theophylline, phenylephrine, ephidrine, pilocarpine, furosemide, tetracycline, chlorpheniramine, ketorolac, ketorolac tromethamine, bromocriptine, guanabenz, prazosin, doxazosin, flufenamic acid, benzonatate, dextromethorphan hydrobromide, noscapine, codeine phosphate, scopolamine, minoxidil, combinations of the above-identified active agents, and pharmaceutically acceptable salts thereof.

Other representative agents include, but are not limited to, benzodiazepines, such as alprazolan, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, flumazenil, flurazepan, halazepan, lorazepan, midazolam, nitrazepan, nordazepan, oxazepan, prazepam, quazepan, temazepan, triazolan, pharmaceutically acceptable salts thereof, and combinations thereof; anticholinergic agents such as anisotropine, atropine, belladonna, clidinium, cyclopentolate, dicyclomine, flavoxate, glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide, mepenzolate, methantheline, oxyphencyclimine, pirenzepine, propantheline, telezepine, tridihexethyl, tropicamide, combinations thereof, and pharmaceutically acceptable salts thereof; estrogens, including but not limited to, 17β–estradiol (or estradiol), 17α-estradiol, chlorotrianisene, methyl estradiol, estriol, equilin, estrone, estropipate, fenestrel, mestranol, quinestrol, estrogen esters (including but not limited to estradiol cypionate, estradiol enanthate, estradiol valerate, estradiol-3-benzoate, estradiol undecylate, and estradiol 16,17-hemisuccinate), ethinyl estradiol, ethinyl estradiol-3-isopropylsulphonate, pharmaceutically acceptable salts thereof, and combinations thereof; androgens such

as danazol, fluoxymesterone, methandrostenolone, methyltestosterone, nandrolone, nandrolone decanoate, nandrolone phenproprionate, oxandrolone, oxymetholone, stanozolol, testolactone, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, 19-nortestosterone, pharmaceutically acceptable salts thereof, and combinations thereof; and progestins such as cingestol, ethynodiol diacetate, gestaclone, gestodene, bydroxyprogesterone caproate, levonorgestrel, medroxyprogesterone acetate, megestrol acetate, norgestimate, 17-deacetyl norgestimate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, desogestrel, progesterone, quingestrone, tigestol, pharmaceutically acceptable salts thereof, and combinations thereof.

An optional enhancer may be combined with the filler prior to the optional blending step, or it may be added to the polymer mixture during the optional blending step, or more preferably during the mixing and heating step. The choice of enhancer to be optionally incorporated in the transdermal drug delivery matrix will depend upon the polymer and active agent to be administered. Suitable enhancers for use in this invention include, but are not limited to, dimethylsulfoxide (DMSO), dimethylformamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C_{10}MSO), polyethylene glycol monolaurate (PEGML), propylene glycol (PG), propylene glycol monolaurate (PGML), methyl laurate, lauryl alcohol, glycerol monolaurate, linoleic acid, oleic acid, oleic acid dimers, oleyl alcohol, glycerol mono-oleate, glycerol dioleate, glycerol trioleate, lauryl lactate, myristyl latate, sorbitan monolaurate, sorbitan mono-oleate, lauramide diethanolamide, lecithin, the 1-substituted azacycloheptan-2-ones (preferably 1-n-dodecylcyclazacycloheptan-2-one, available under the trademark Azone® from Whitby Research Inc., Richmond, VA), alcohols, lactate esters of C_{12} to C_{18} aliphatic alcohols, and the like. The permeation enhancer may also be a vegetable oil, as described in U.S. Pat. No. 5,229,130 to Sharma et al.. Such oils include, by way of example and not for purposes of limitation, safflower oil, cotton seed oil and corn oil. In addition, combinations of enhancers as enumerated above, or as described in U.S. Pat. No. 5,053,227 to Chiang et al. and U.S. Pat. No. 5,693,335 to Xia et al., may be used in the present invention.

The amount of enhancer present in the composition will depend on a number of factors, e.g. the strength of the particular enhancer, the desired increase in skin

permeability, the rate of administration, and the type and amount of active agent to be delivered. The enhanced permeation effected through the use of such enhancers can be observed by measuring the rate of diffusion of active agent through animal or human skin using a Franz diffusion cell apparatus as described in U.S. 5,807,570 to Chen et al. Such determinations are easily made by one of ordinary skill in the art (see, for example, Volume 62 of Drugs and the Pharmaceutical Sciences, titled "Drug Permeation Enhancement: Theory and Applications" (1994) Marcel Dekker, Inc.).

Tackifiers, which may comprise either natural resinous or rosinous materials or synthetic substances, also may be optionally incorporated into the polymer mixture for the purpose of making the adhesive polymer more "tacky." Examples of suitable tackifiers include, but are not limited to, aliphatic hydrocarbons, substituted and unsubstituted aromatic hydrocarbons, hydrogenated esters, polyterpines, hydrogenated wood resins, mineral oil, and high T_g, low molecular weight aliphatic resins such as ESCOREZ™ resins (Exxon Chemical), and mixtures thereof. Preferred tackifiers include, but are not limited to, mineral oil or polybutene.

Suitable plasticizers for optional use in the method of the present invention include, but are not limited to the following: mineral oil; animal and vegetable oils including but not limited to olive oil, safflower oil, coconut oil and triglyceride fatty acids; hydrocarbons including but not limited to polybutene and squalene; alcohols including but not limited to butanediol; PGML, oleic acid dimers (for example, linoleic acid dimer); lauric acid; and monohydric alcohol fatty acid esters including but not limited to octanoic acid cetyl ester, myristyl lactate, and lauryl lactate. Preferred plasticizers include, but are not limited to, mineral oil or polybutene.

If the blending step of the method of the present invention is performed, the polymer and filler may be combined in a blending or premixing step. The polymer mixture prepared by the blending step is then added, via the main feeder, into one end of the multiple-lobed compounder. Alternatively, the polymer mixture components may be added to the main feeder without blending the components. The compounder comprises modular components, each of which comprises chambers and lobed elements. The interaction of the lobe interfaces during rotation of the lobed elements within the chamber provides the continuous dispersive mixing of the method of the

present invention. Secondary feeder stations as well as injection ports may be present on the compounder to allow the admixing of additional polymer mixture components.

Any portions of filler or excipients that were not mixed into the polymer mixture during the above-described blending step may be metered onto these additional stations on the compounder and introduced into the polymer mixture. In addition, if the active agent was not added to the polymer mixture during the blending step, the agent may be introduced into the polymer mixture during the initial heating and mixing step, or even after the mixing and heating step has started.

The polymer mixture is continuously mixed and heated as it moves along each module down the length of the compounder. Speed of travel of the polymer mixture is determined by the design of the lobed element and the rate of polymer being fed into the main feeder. The temperature at which the heating steps is performed may vary with the choice of polymer and active agent, but generally will range from about 60°C to about 200°C, preferably between about 80°C and about 170°C. The more preferred ranges are selected from the following: about 80°C to about 100°C, about 100°C to about 130°C, about 130°C to about 150°C, and about 150°C to about 180°C. The speed at which the polymer traverses the length of the compounder may be controlled, as may the temperature, to minimize any degradation of the components of the transdermal device.

After completing the mixing and heating step, the polymer mixture is then extruded from the compounder, usually via one or more dies. To provide a uniform flow of the extrudate during this step, a gear pump may be installed between the compounder and the die. The extrudate is forced through the die and collected on a surface during the forming step. The extrudate is usually placed between a release liner and a second layer (for example, a backing layer or porous supporting layer) during the forming step. However, the second layer may be omitted and the extrudate may be placed on a single surface. The thickness of the extrudate will depend upon the choice of polymers, active agents, and enhancers incorporated into the transdermal matrix, such that a therapeutically effective amount of active agent will be administered during use of the matrix in a drug delivery device. In general, the final thickness of the extrudate may range from about 5 μm (0.2 mils) to about 1 mm (40 mils), preferably ranging from about 10 μm (0.4 mils) to about 500 μm (20 mils),

more preferably ranging from about 20 μm (0.8 mils) to about 250 μm (10 mils). Depending upon the temperature used during the mixing and heating step, the extrudate collected during the forming step may be chilled while winding the laminate into a roll for further processing.

The backing layer of the transdermal drug delivery device is generally chosen from materials that are impermeable to the active agent and any excipients of the matrix. This layer may be made from a single layer of film or polymer, or it may comprise a laminate of one or more material layers. Backing layers suitable for use in the present invention may be chosen from materials including but not limited to acrylonitrile, cellophane, cellulose derivatives including but not limited to cellulose acetate and ethylcellulose, ethylene vinyl alcohol, ethylene vinyl acetate, synthetic fabrics (including but not limited to nylon, rayon and polyester), polyethylene, polyethylene terephthalate, polypropylene, polyether amides, polyvinyl alcohol, polyvinyl chloride, polyvinylidene chloride, polyvinyl terephthalate, polycarbonate, polystyrene, polyurethane, polyolefins including but not limited to ethylene-vinyl acetate copolymers, flexible fibrous materials such as paper and cloth, metalized polyester films, metalized plastics, and metallic foils. The backing layer may also be prepared as described in U.S. Pat. No. 5,246,705 to Venkatraman for an occlusive, elastomeric backing material. If the transdermal device is to be used on a long term basis, such as for multiple days, the backing may be perforated in a manner to permit the passage of air and water, and thus minimize skin hydration and loss of the adhesive properties of the device.

A release liner may be used to protect the transdermal matrix during processing, or to protect the basal surface of the transdermal device prior to use . Similar to the backing layer, the release liner may comprise a single layer of film or polymer, or a laminate of one or more material layers. Typically these liners are formed from materials impermeable to the active agent, or else are treated with silicone or fluorocarbons. Release liners suitable for use in the present invention may be chosen from materials including but not limited to silicone- or fluropolymer-coated polyesters, polyethylenes, and polypropylenes.

A porous supporting layer may be optionally incorporated into the transdermal device to reduce the "cold flow" of the polymer, or to act as a site for deposition of

liquid matrix components. Suitable materials that may be employed as the porous supporting layer include, but are not limited to, polyester nonwoven and mesh.

It may also be desirable to include an optional rate-controlling membrane, particularly in the manufacture of the "reservoir"-style transdermal drug delivery matrices. Suitable materials include, but are not limited to, polyolefins (for example polyethylene and polypropylene), polyamides, polyesters, ethylene-propylene copolymer, ethylene ethacrylate copolymer, ethylene-vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene, polyacrylonitrile, and the like.

In the forming step, a portion of the resulting extruded polymer mixture (i.e. the laminate of extrudate and liners) is formed into transdermal drug delivery matrix. Single or multiple coating passes may be prepared in the method of the present invention, using the same or multiple polymer mixtures. A single coating pass may be laminated between two layers, for example a release liner and a backing layer. If the polymer is not an adhesive, the polymer mixture may be coated onto a single layer (for example, a release liner). Two coating passes may be performed using the method of the present invention, one in which the extrudate is layered between a backing layer and a release liner, the second in which the extrudate is layered between a porous supporting layer and a release liner. In the incorporating step, the release liner from the first coating pass is removed and the exposed extrudate is laminated to the porous supporting layer of the second coating pass, sandwiching the porous supporting layer between the two extrudates. The resulting laminate may be cut using a rotary die cutting system, to form a patch of the size necessary to administer a therapeutically effective amount of the active agent. Such determinations are easily made by one of ordinary skill in the art (see, for example, Volume 18 of Drugs and the Pharmaceutical Sciences, titled "Dermatological Formulations: Percutaneous Absorption" (1983) Marcel Dekker, Inc.). The transdermal devices thus formed may be optionally pouched (for example, using paper-poly-foil) and sealed for storage purposes.

In the manufacture of the transdermal drug delivery devices, transdermal sampling devices and dermal conditioning devices, the step of incorporating the polymeric matrix into the drug delivery, sampling or conditioning device may involve

further manipulation of the polymeric matrix. In some cases, it may be desirable to shape a portion of the polymeric matrix into microscopic needle-like projections, or microneedles. These microneedles, when positioned on the means of securing side of the dermal conditioning device, may be inserted into the uppermost surface layer of the skin or mucosa, while not causing marked disruption of the underlying dermis layers. The microneedle structures may be formed, for example, by pressing a mold with one or multiple projections against the extrudate to form the desired projections. This step may be performed at any point between the extruding step and the pouching of the manufactured transdermal device.

EXAMPLES

The following examples illustrate the present invention and are not meant to be limitations of the scope of the invention. The composition of the polymers produced by the present method of manufacture will, of course, vary depending upon the polymers, active agents and optional excipients to be incorporated. These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the methods of manufacture, as well as the usage and formulations as more fully set forth below.

Example 1: Manufacture of a transdermal drug delivery matrix containing olanzapine.

An olanzapine transdermal drug delivery matrix was prepared using a 27 mm twin screw extruder (American Leistritz Extruder Corporation of Somerville, NJ) as follows: 427 grams (g) of HMW polyisobutylene (Vistanex L80 from Exxon Chemicals, Linden, NJ) were transferred to a high shear Sigma blade mixer (Jaygo, Inc., Union, NJ). Alternating portions of the LMW polyisobutylene (855 g, Vistanex LM-MS-LC, also from Exxon Chemicals, Linden, NJ), silica gel powder (165 g Silica Gel 244 FP Syloid powder from W. R. Grace & Co., Baltimore, MD) and PVP-CLM (165 g Kollidone® from BASF, Germany) were added to the HMW polyisobutylene, followed by 855 grams of polybutene (Amoco Chemical Co., Whiting, IN), all while mixing continuously at about 70-80°C. The polyisobutylene polymer blend was metered onto the main feeder of the twin screw extruder, while the olanzapine (50 g) and lauryl lactate (340 g) were metered onto adjacent stations. The components were

mixed and heated in the compounder at temperatures between 90-130°C. After traversing the length of the compounder, the resulting polymeric mixture was extruded through a sheet die, and coated between a release liner and a backing material. A gear pump was positioned between the twin screw extruder and the extrusion die, in order to ensure a uniform coating of the extruded polymer mixture onto the release liner. The cross-section of the extrudate is fixed by the dimensions of the die used, to produce a matrix that is, for example, about 10 mm wide by about 3 mils (0.075 mm) thick. A second layer of this same extrudate was coated between a second release liner and a polyester nonwoven porous supporting layer. The release liner from the first coating pass was removed and the exposed extrudate was laminated to the nonwoven side of the second coating pass, sandwiching the porous supporting layer between the two extrudates. The rolls of laminate were converted to transdermal devices of the desired size (in this example, 40 cm^2) using a rotary die cutting system. The transdermal devices were then pouched using paper-poly-foil and sealed.

In the manufacture of olanzapine-containing transdermal matrices, it was determined that the PVP-CLM may be replaced with microcrystalline cellulose, ethyl cellulose, methyl cellulose or combinations thereof. Escorex™ tackifier (Exxon Chemicals) may be used in place of the polybutene. In addition, instead of preparing two separate extrudates and laminating them with the porous supporting layer in the center, the transdermal matrix may have been prepared as a single extrudate, by coextruding the polymer mixture with fibers and placing the resulting extrudate between the backing layer and the release liner.

Example 2: Manufacture of a transdermal drug delivery matrix containing tamsulosin.

A tamsulosin transdermal drug delivery matrix was prepared, using a Werner and Fleiderer ZSK-30 twin screw extruder, as follows: 13.2 kilograms (kg) of HMW polyisobutylene and a portion (3.1 kg) of the silica gel powder were blended at 70-80°C in a Sigma blade mixer, while adding alternating portions of the LMW polyisobutylene (26.4 kg) and the remaining silica gel powder (12.3 kg). The addition of these components was followed by the addition of 26 kg of polybutene. The polymer mixture, approximately 42 g of tamsulosin and 400 g of polybutene

(EMPOL®, Amoco Chemicals) were metered onto different stations on the twin screw extruder, and the components were mixed together at temperatures between 90-130°C. After the polymer mixture had traversed the length of the compounder, the resulting formulation was extruded as described in Example 1. The rolls of laminate were converted to transdermal matrices of the desired size (in this example, 38 cm^2) using a rotary die cutting system. The transdermal devices were then pouched using paper-poly-foil and sealed. In additional experiments, it was determined that microcrystalline cellulose may be substituted for the PVP-CLM, and oleic acid dimers or lauric acid may be added to the formulation as solubilizers. As with the previous example, the transdermal matrix may have been prepared by coextruding the polymer mixture with fibers, and placing the extrudate between the backing layer and the release liner.

Example 3: Manufacture of a transdermal drug delivery matrix containing a contraceptive.

A contraceptive transdermal drug delivery matrix is prepared using a multiple-lobed compounder as follows. The HMW polyisobutylene is transferred to a high shear mixer with a first portion (about 20% of the total) of the PVP-CLM. While blending these components, alternating portions of LMW polyisobutylene and the remaining PVP-CLM are added to the polymer mixture, followed by polybutene, while maintaining the temperature continuously at about 100°C. The polymer mixture is then metered into the main feeder of the multiple-lobed compounder, the contraceptive agents and any optional enhancers are metered onto adjacent stations, and the components are mixed while heating to temperatures of about 130°C. After the components have traversed the length of the extruder, the resulting polymer mixture is extruded and formed into transdermal devices as described in the previous examples.

The contraceptive agent comprises an estrogen, a progestin, or an estrogen/progestin combination, and may include, but is not limited to preferred estrogens and progestins such as 17β-estradiol, 17α-estradiol, ethinyl estradiol, mestranol, quinestrol, estrone, equilin, progesterone, testosterone, 19-nortestosterone, norethindrone, norethindrone actetate, norgestrel, levonorgestrel, desogestrel,

norgestimate, 17-deacetyl norgestimate, pharmaceutically acceptable salts thereof, and combinations thereof. Preferred enhancers for a contraceptive transdermal drug delivery matrix include, by way of example and not for purposes of limitation, butanediol, lauryl lactate, myristyl lactate, propylene glycol, polyethylene glycol (for example, PEG-400), hexylene glycol, diethylene glycol, or any combination of the above. A particularly preferred formulation of a contraceptive transdermal drug delivery matrix comprises the contraceptive active agents 17-deacetyl norgestimate and ethinyl estradiol and the enhancer comprises lauryl lactate, diethylene glycol and combinations thereof. As with the previous examples, the transdermal matrix may be prepared by coextruding the polymer mixture with fibers, and placing the extrudate between the backing layer and the release liner.

Example 4: Manufacture of a transdermal drug delivery matrix containing felodipine.

A felodipine-containing transdermal drug delivery matrix is prepared substantially as described for the previous examples. The HMW polyisobutylene, LMW polyisobutylene, silica gel powder, PVP-CLM, and polybutene are combined as described in Example 1 while mixing continuously at about 80 to about100°C. Then the polymer mixture, felodipine, and optional enhancer are metered onto different stations on the multiple lobed compounder and the processed at about 80 to about100°C. The resulting extrudate is formed into transdermal devices as described for Example 1.

Example 5: Manufacture of a transdermal drug delivery matrix containing clonazepam.

A clonazipan-containing transdermal drug delivery matrix is prepared substantially as described for the previous examples. The HMW polyisobutylene, LMW polyisobutylene, silica gel powder, PVP-CLM and polybutene are combined as described in Example 1 while mixing continuously at about 80 to about 100°C. Then the polymer mixture, clonazipan powder, and desired enhancer are metered onto different stations on the multiple lobed compounder and processed at about 80 to about 100°C. The resulting extrudate is formed into transdermal devices as described for Example 1.

Example 6: Transmucosal drug delivery device containing a breath freshening compound.

A transmucosal drug delivery device containing a breath freshening compound is prepared substantially as described for the previous examples, except that during the forming step, the extrudate is placed upon a release liner in the absence of a backing layer. The hydroxypropyl cellulose, the polyvinylpyrrolidone, and the breath freshening compound (peppermint oil, spearmint oil, wintergreen oil, menthol, or a combination thereof) are metered onto different stations on the multiple lobed compounder. The mixing and heating step are performed at about 80 to about120°C, and the resulting extrudate collected on a release liner and formed into transmucosal devices. The breath freshening compounds may be added toward the end of the mixing and heating step, to reduce the loss of these volatile active agents during the manufacturing process.

Example 7: Transmucosal drug delivery device containing an anesthetic.

A transmucosal drug delivery device containing an anesthetic is prepared substantially as described for Example 6. The hydroxypropyl cellulose, the polyvinylpyrrolidone, and the local anesthetic (e.g. benzocaine, lidocaine, tetracaine, dyclonine, isobutamben, zolamine hydrochloride or combinations thereof) are metered onto different stations on the multiple lobed compounder. The mixing and heating step are performed at about 80 to about 120°C, and the resulting extrudate collected on a release liner and formed into transmucosal devices. The anesthetic agents may be added toward the end of the mixing and heating step, to reduce the loss of these volatile active agents during the manufacturing process.

Example 8: Transmucosal drug delivery device containing a sore throat medicament.

A transmucosal drug delivery device containing a sore throat medicament is prepared substantially as described for Example 6. The hydroxypropyl cellulose, the polyvinylpyrrolidone, and the sore throat medicament (dextromethorphan hydrobromide, noscapine, codeine phosphate, menthol, or combinations thereof) are metered onto different stations on the multiple lobed compounder. The mixing and

heating step are performed at about 80 to about120°C, and the resulting extrudate collected on a release liner and formed into transmucosal devices. The medicaments may be added toward the end of the mixing and heating step, to reduce the loss of any volatile components during the manufacturing process.

Example 9: Manufacture of a transdermal sampling device.

A transdermal sampling device is prepared substantially as described for the previous transdermal drug delivery devices. The polyethylene oxide, filler and optional excipients are combined as described in Example 1, while mixing continuously at between about 100°C to about180°C. Then the polymer mixture and any desired reactants (substrates or enzymes, for example) are metered onto different stations on the multiple-lobed compounder and processed at about 100 to about 180°C. The resulting extrudate is pressed against a mold to form a plurality of microprojections. The microprojections may be solid or hollow, depending upon the mold used. The molded extrudate is then collected between a backing layer and a release liner. Additional reactant may be added to the transdermal matrix, adjacent to the microprojections. . In addition, fibers may be incorporated, or embedded, into the polymer mixture during the mixing and heating, or during the blending prior to the mixing and heating.

Example 10: Manufacture of a dermal conditioning device.

A dermal conditioning device is prepared substantially as described for the previous transdermal drug delivery devices. The crystalline polymer, filler, and optional excipients are combined as described in Example 1, while mixing continuously at between about 90 to about 170°C. Then the polymer mixture and an active agent (for example, an anesthetic) are metered onto different stations on the multiple lobed compounder and processed at about 90 to about 170°C. The resulting extrudate is pressed against a mold to form a plurality of microprojections, then collected between a backing layer and a release liner. As with the transdermal sampling device, the microprojections formed in the dermal conditioning matrix may be solid or hollow, depending upon the mold used, and additional active agents may

be added to the matrix. . In addition, fibers may be incorporated, or embedded, into the polymer mixture during the mixing and heating, or during the blending prior to the mixing and heating.

What is claimed is:

1. A method of manufacturing a transdermal drug delivery matrix, the method comprising:

(a) mixing and heating a polymer and an active agent in a multiple-lobed compounder to produce a polymer mixture;

(b) extruding the polymer mixture; and

(c) forming at least a portion of the resulting extruded polymer mixture into a transdermal drug delivery matrix.

2. The method of claim 1, wherein the heating step is performed at about 80°C to about 170°C.

3. The method of claim 2, wherein the heating step is performed at about 100°C to about 130°C.

4. The method of claim 1, wherein the polymer mixture further comprises a filler.

5. The method of claim 1, wherein the polymer comprises a pressure-sensitive adhesive.

6. The method of claim 5 wherein the pressure-sensitive adhesive comprises polyisobutylene.

7. The method of claim 6, wherein the polyisobutylene comprises a mixture of between about 25% to about 95 % by weight low molecular weight polyisobutylene (LMW PIB) and between about 5% and about 75% by weight high molecular weight polyisobutylene (HMW PIB).

8. The method of claim 7, wherein the polyisobutylene comprises a mixture of about 67% LMW PIB and about 33% HMW PIB.

9. The method of claim 1, wherein the polymer mixture further comprises an enhancer.

10. The method of claim 1, wherein the active agent is selected from the group consisting of ACE inhibitors, adrenergics, alcohol deterents, analgesics, anesthetics, anti-adrenergics, anti-allergics, anti-anginals, anti-anxiety preparations, anti-arrhythmics, anti-arthritics, anti-asthmatics, antibiotics, anticholinergics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antidiarrheals, anti-emetics, anti-epileptics, anti-fungals, antihelminthics, antihistamines, antihypertensives, anti-inflammatory agents, antimalarials, antimigraines, antinauseants, antineoplastics, antioxidants, antiparkinsonians, antipruritics, antipsychotics, antipyretics, antirheumatics, antispasmodics, antitussives, antivirals, appetite suppressants, anorexics, anxiolytics, breath fresheners, calcium channel blockers, cardiac depressants, cardiotonics, cholinergics, contraceptives, cough and cold preparations, decongestants, diuretics, growth stimulants, herbal preparations, hormones, hypnotics, immunizing agents, immunomodulators, immunosuppresives, muscle relaxants, psychostimulants, sedatives, sore throat medicaments, steroids, sympathomimetics, tranquilizers, vaccines, vasodilators, vitamins, xanthine derivatives, and combinations thereof.

11. The method of claim 10, wherein the active agent comprises a hormone selected from the group consisting of 17β-estradiol, 17α-estradiol, ethinyl estradiol, mestranol, quinestrol, estrone, equilin, progesterone, testosterone, 19-nortestosterone, norethindrone, norethindrone actetate, norgestrel, levonorgestrel, desogestrel, norgestimate, 17-deacetyl norgestimate, pharmaceutically acceptable salts thereof, and combinations thereof.

12. The method of claim 10, wherein the active agent comprises a vasodilator comprising felodipine.

13. The method of claim 10, wherein the active agent comprises an anticonvulsant comprising clonazepam.

14. The method of claim 1, wherein the multiple-lobed compounder comprises a twin screw extruder.

15. The method of claim 1, wherein the multiple-lobed compounder comprises a continuous kneader.

16. A method of manufacturing a transdermal drug delivery matrix, the method comprising:

(a) blending a polymer and an active agent to produce a polymer mixture;

(b) mixing and heating the polymer mixture in a multiple-lobed compounder;

(c) extruding the polymer mixture; and

(d) forming at least a portion of the resulting extruded polymer mixture into a transdermal drug delivery matrix.

17. The method of claim 16, wherein the polymer mixture further comprises a filler.

18. The method of claim 16, wherein the polymer comprises a pressure-sensitive adhesive.

19. The method of claim 18 wherein the pressure-sensitive adhesive polymer comprises polyisobutylene.

20. The method of claim 19, wherein the polyisobutylene comprises a mixture of between about 25% to about 95 % by weight LMW PIB and between about 5% and about 75% by weight HMW PIB.

21. The method of claim 20, wherein the polyisobutylene comprises a mixture of about 67% by weight of LMW PIB and about 33% by weight of HMW PIB.

22. The method of claim 16, wherein the polymer mixture further comprises an enhancer.

23. The method of claim 16, wherein the active agent is selected from the group consisting of ACE inhibitors, adrenergics, alcohol deterents, analgesics, anesthetics, anti-adrenergics, anti-allergics, anti-anginals, anti-anxiety preparations, anti-arrhythmics, anti-arthritics, anti-asthmatics, antibiotics, anticholinergics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antidiarrheals, anti-emetics, anti-epileptics, anti-fungals, antihelminthics, antihistamines, antihypertensives, anti-inflammatory agents, antimalarials, antimigraines, antinauseants, antineoplastics, antioxidants, antiparkinsonians, antipruritics, antipsychotics, antipyretics, antirheumatics, antispasmodics, antitussives, antivirals, appetite suppressants, anorexics, anxiolytics, breath fresheners, calcium channel blockers, cardiac depressants, cardiotonics, cholinergics, contraceptives, cough and cold preparations, decongestants, diuretics, growth stimulants, herbal preparations, hormones, hypnotics, immunizing agents, immunomodulators, immunosuppresives, muscle relaxants, psychostimulants, sedatives, sore throat medicaments, steroids, sympathomimetics, tranquilizers, vaccines, vasodilators, vitamins, xanthine derivatives, and combinations thereof.

24. The method of claim 23, wherein the active agent comprises a hormone selected from the group consisting of 17β-estradiol, 17α-estradiol, ethinyl estradiol, mestranol, quinestrol, estrone, equilin, progesterone, testosterone, 19-nortestosterone, norethindrone, norethindrone actetate, norgestrel, levonorgestrel, desogestrel, norgestimate, 17-deacetyl norgestimate, pharmaceutically acceptable salts thereof, and combinations thereof.

25. A method of manufacturing a contraceptive transdermal drug delivery matrix, the method comprising:

(a) blending a pressure-sensitive adhesive, a first portion of a filler, and a hormone to produce a polymer mixture;

(b) mixing and heating the polymer mixture and a second portion of the filler in a multiple-lobed compounder;

(c) extruding the polymer mixture; and

(d) forming at least a portion of the resulting extruded polymer mixture into a contraceptive transdermal drug delivery matrix.

26. The method of claim 25, wherein the polymer mixture further comprises an enhancer selected from the group consisting of lauryl lactate, methyl lactate, diethylene glycol, propylene glycol monolaurate, C_{12} to C_{18} aliphatic alcohols, and combinations thereof.

27. The method of claim 26, wherein the pressure sensitive adhesive comprises polyisobutylene, the hormone comprises a progestin and an estrogen, the filler comprises polyvinylpyrrolidone, and the enhancer is selected from the group consisting of lauryl lactate, diethylene glycol, and combinations thereof.

28. The method of claim 27, wherein the progestin comprises 17-deacetyl norgestimate and the estrogen comprises ethinyl estradiol.

29. A method of manufacturing a transmucosal drug delivery device, the method comprising:

(a) blending a water-soluble polymer, a first portion of a filler, and an active agent to produce a polymer mixture;

(b) mixing and heating the polymer mixture and a second portion of the filler in a multiple-lobed compounder;

(c) extruding the polymer mixture; and

(d) incorporating at least a portion of the resulting extruded polymer mixture into a transmucosal drug delivery device.

30. The method of claim 29, wherein the water-soluble polymer comprises hydroxypropyl cellulose, the filler comprises polyvinylpyrrolidone, and the active agent comprises a breath freshening compound selected from the group consisting of peppermint oil, spearmint oil, wintergreen oil, menthol, and combinations thereof.

31. The method of claim 29, wherein the water-soluble polymer comprises hydroxypropyl cellulose, the filler comprises polyvinylpyrrolidone, and the active agent comprises an anesthetic selected from the group consisting of benzocaine, lidocaine, tetracaine, dyclonine, isobutamben, zolamine hydrochloride, and combinations thereof.

32. The method of claim 29, wherein the water-soluble polymer comprises hydroxypropyl cellulose, the filler comprises polyvinylpyrrolidone, and the active agent comprises a sore throat medicament selected from the group consisting of dextromethorphan hydrobromide, noscapine, codeine phosphate, menthol, and combinations thereof.

33. A method of manufacturing a transdermal drug delivery device, the method comprising:

(a) mixing and heating a polymer and an active agent in a multiple-lobed compounder to produce a polymer mixture;

(b) extruding the polymer mixture; and

(c) incorporating at least a portion of the resulting extruded polymer mixture into a transdermal drug delivery device.

34. A transdermal drug delivery matrix produced according to the method of claim 1.

35. A transdermal drug delivery matrix produced according to the method of claim 16.

36. A contraceptive transdermal drug delivery device produced according to the method of claim 25.

37. A transmucosal drug delivery device produced according to the method of claim 30.

38. A transmucosal drug delivery device produced according to the method of claim 31.

39. A transmucosal drug delivery device produced according to the method of claim 32.

40. A transdermal drug delivery device produced according to the method of claim 33.

41. A method of delivering an active agent to a subject comprising transdermally administering the matrix of claim 34.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 00/02491

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y A	page 3, line 61 -page 5, line 5 claim 1	4,6-9 25,36
X	EP 0 598 606 A (JOHNSON & JOHNSON CONSUMER PRODUCTS, INC.) 25 May 1994 (1994-05-25)	1,2,10, 14
A	page 6, line 34 - line 56 page 8 -page 9; example 5	15,16
Y	WO 98 37872 A (CYGNUS, INC.) 3 September 1998 (1998-09-03) page 10, line 4 -page 11, line 12 page 16, line 1 - line 25	4,6-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2000	11/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
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